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# Fungal Lectins: Current Molecular and Biochemical Perspectives

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## ABSTRACT

The aim of this study is to provide concise information about recent developments in understanding of fungal lectins. Lectins, a well-known class of multivalent carbohydrate binding proteins of non-immune origin that recognize diverse sugar structures with a high degree of stereospecificity in a non-catalytic manner are wide spread in distribution. Plant and animal lectins are subjected to extensive studies and only limited information was available on fungal lectins. In last few years mushroom and other fungal lectins have attracted wide attention due to their antitumor, antiproliferative and immunomodulatory activities. Earlier fungal lectin reports deal only with their purification, carbohydrate specificity, basic characterization and possible roles. In last ten years, several fungal lectins have been cloned, sequenced and crystallized. More subtle information about their structure and binding properties is available, obtained by employing more advanced techniques such as X-ray crystallography, surface plasmon resonance and enzyme linked lectinsorbent assay etc. Several fungal lectins have been discovered in the recent years and their structural and biochemical properties have been explored. However, some of them show resemblance with plant and bacterial lectins, but still there are enough evidence to place them in a diverse lectin group. This article will provide concise information about recent advancement in understanding of fungal lectins regarding their biochemical and molecular properties.

**Key words:** Protein structure, fungi, hemagglutinin, glycochemistry, purification, SPR

## INTRODUCTION

Lectins, a well-known class of multivalent carbohydrate binding proteins of non-immune origin which recognize diverse sugar structures with a high degree of stereospecificity in a non-catalytic manner are wide spread in distribution (Sharon and Lis, 1989).

Lectins have been implicated in cellular signaling, malignancy, host pathogen interactions, scavenging of glycoproteins from the circulatory system, cell-cell interactions in the immune system, differentiation and protein targeting to cellular compartments (Ashwell and Harford, 1982; Sharon and Lis, 1989; Springer and Lasky, 1991). Plant and animal lectins are subjected to extensive studies (Rini and Lobsanov, 1999; Rudiger and Gabiu, 2001; Occena *et al*., 2007; Tanaka *et al*., 2009; Fujii *et al*., 2009; Kaur *et al*., 2006) and very little information is available on lectins from fungi (Guillot and Konska, 1997; Konska, 2006; Wang *et al*., 1998). However, first fungal lectin phallin was reported by Kobert in 1891 from *Amanita phalloides*, which was a hemolytic agent (Horejsi and Kocourek, 1978) and later a fungal hemagglutinin was discovered in the fly agaric (Ford, 1910). In last few years mushroom and other fungal lectins have attracted wide attention due to their antitumor, antiproliferative and immunomodulatory activities (She *et al*., 1998;

Wang *et al.*, 2000; Waiser and Weis, 1999). More recently, there are several reports on lectins from lower and pathogenic fungi but their physiological role still remains uncertain (Candy *et al.*, 2001, 2003; Khan *et al.*, 2007c; Tronchin *et al.*, 2002; Wu *et al.*, 2001).

There are few reviews about fungal and mushroom lectins (Guillot and Konska, 1997; Konska, 2006; Singh *et al.*, 2010; Wang *et al.*, 1998) till date, mainly dealing about their taxonomic and biological perspectives. This article will provide concise but exclusive information regarding advancement in understanding of fungal lectins about their biochemical and molecular aspects as proteins.

Relevant abstracts and references were collected from PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Science Alert (http://scialert.net/index.php). Sequence alignment studies were carried out by obtaining amino acid sequences of the lectins from NCBI (http://www.ncbi.nlm.nih.gov/protein) and aligned by ClustalW2 (http://www.ebi.ac.uk/Tools/clustalw2/index.html).

## FUNGAL LECTINS

**Occurrence and localization:** Fungal lectins have been isolated from mycelium (Candy *et al.*, 2003; Khan *et al.*, 2007c), conidia (Tronchin *et al.*, 2002), sporomes (Guillot and Konska, 1997) basidiomes (Guillot and Konska, 1997) and fruiting bodies (Thakur *et al.*, 2007b; Wang and Ng, 2003) whereas, lectin from pathogenic fungus *Macrophomina phaseolina* is extracellular in nature (Bhowal *et al.*, 2005). In case of few strains of *Rhizoctonia solani*, the amount of lectin in the sclerotia was higher than in the mycelium (Hamshou *et al.*, 2007).

**Detection and assay:** Lectins were earlier discovered as hemagglutinating agents and hemagglutination is still a universally adopted and easiest detection technique of the lectin activity in crude or purified protein extracts. The hemagglutination assay is carried out using animal as well as human erythrocytes (Khan *et al.*, 2007c; Thakur *et al.*, 2007b). Sometimes erythrocytes are treated with enzymes like pronase, trypsin, papain and neuraminidase or any other proteolytic enzyme (Khan *et al.*, 2007c; Thakur *et al.*, 2007b). Other types of cells like lymphocytes, sperms and yeast have also been used for lectin detection (Nicolson, 1974). Lectins also form cross-links between polysaccharide (Chien *et al.*, 1975; Van Wauwe *et al.*, 1973) or glycoproteins (Yachnin, 1972, 1975) in solution and induce their precipitation.

**Purification:** Since, majority of fungal lectins are intracellular, most of the purification procedures, involves lysis of cells by some physical method, followed by conventional protein purification techniques such as chromatography using various resins.

Ion-exchangers like DEAE- CM-cellulose and QAE-Toyopearl, most readily available resins, have been used for the purification of some fungal lectins (Kossowska *et al.*, 1999; Li *et al.*, 2008; Zhao *et al.*, 2009). Gel filtration has been used as one of the purification steps for lectins from *Rhizopus stolonifer* (Oda *et al.*, 2003) and *Aspergillus fumigatus* (Tronchin *et al.*, 2002). In addition, hydrophobic matrix like Phenyl-Sepharose has been employed for the purification of lectins from *A. fumigatus* (Tronchin *et al.*, 2002), *Beauveria Bassiana* (Kossowska *et al.*, 1999) and *Fusarium solani* (Khan *et al.*, 2007c).

Affinity chromatography, as more specific technique for lectin purification, has been extensively used for purification of fungal lectins. Several affinity resins have been generated and used according to the lectin specificity such as fetuin-Sepharose (Bhowal *et al.*, 2005), BSM-Toyopearl (Kawagishi *et al.*, 1997), PSM-Sepharose (Chumkhunthod *et al.*, 2006), lactosyl-Sepharose

(Pohleven *et al.*, 2009) and gal-Sepharose (Candy *et al.*, 2003). In some cases, Sephadex and Sepharose or acid treated Sepharose have been used to purify glucopyranosyl/mannopyranosyl and galactopyranoside binding lectins respectively, where they serve as affinity matrix and not as molecular sieves. Sepharose was used for the isolation of a lectin from *Ischnoderma resinosum*, specific for methyl β-galactoside (Kawagishi and Mizuno, 1988). The intracellular lectin, calnexin, from *Aspergillus oryzae* was purified from conjugating synthetic N-linked glycan to Sepharose beads (Watanabe *et al.*, 2007). In some cases, ability of lectins to agglutinate erythrocytes has been utilized for their purification, by embedding erythrocytes or erythrocyte stromas in polyacrylamide (Guillot *et al.*, 1983).

Modern purification techniques like HPLC and FPLC have also been employed for the purification of lectins from *Hygrophorus hypothejus* (Veau *et al.*, 1999), *Ganoderma capense* (Ngai and Ng, 2004), *Peziza sylvestris* (Wang and Ng, 2005) and *Pholiota adiposa* (Zhang *et al.*, 2009). Recombinant lectin of *Agrocybe aegerita* is expressed in *E. coli* based expression system with addition of the Histidine tag and purified using Ni-column chromatography (Yang *et al.*, 2005a).

**Molecular mass and subunit structure:** Molecular masses of fungal lectins range from 15-90 kDa, but majority of them are between 23-36 kDa (Table 1). In general, most of them are dimeric proteins and subunits are held together by non-covalent interactions, with few exceptions

Table 1: Physical properties of some fungal lectins

| Source | Molecular mass (kDa) | Sub-unit type | pI | Carbohydrate content (%) | Specificity | References |
|---|---|---|---|---|---|---|
| *Agaricus blazei* | 70 | $\alpha_4$ | | 11.0 | Glycoproteins | Kawagishi *et al.* (1988) |
| *Arthrobotrys oligospora* | 36 | $\alpha_2$ | 6.5 | | | Rosen *et al.* (1992) |
| *Auricularia polytricha* | 23 | α | 10.6 | 3.5 | | Yagi and Tadera (1988) |
| *Amanita pantherina* | 43 | $\alpha_2$ | - | 4.3 | Mucin | Zhuang *et al.* (1996) |
| *Beauveria bassiana* | 15 | α | 7.1 | 12.6 | Glycoproteins | Kossowska *et al.* (1999) |
| *Chlorophyllum molybdites* | 32 | $\alpha_2$ | 3.75 | 12.0 | | Kobayashi *et al.* (2004) |
| *Clitocybe nebularis* | 33 | $\alpha_2$ | 4.3 | - | Asialo-fetuin and lactose | Pohleven *et al.* (2009) |
| *Clitocybe nebularis* | 30 | $\alpha_2$ | 4.3 | 10.0 | D-Galactose | Horejsi and Kocourek (1978) |
| *Fusarium solani* | 26 | $\alpha_2$ | 8.7 | 3.9 | Glycoproteins | Khan *et al.* (2007c) |
| *Hygrophorus hypothejus* | 68 | $\alpha_4$ | 5.0 | 0.0 | | Veau *et al.* (1999) |
| *Ischnoderma resinosum* | 32 | $\alpha_2$ | 5.5 | 4.0 | | Kawagishi and Mizuno (1988) |
| *Laccaria amethystea* | 16 | α | 9.5 | 0.0 | L-Fucose, Lactose | Guillot *et al.* (1983) |
| *Lactarius deliciosus* | 37 | αβ | 6.7 | 0.0 | Galβ1→3GalNAc | Guillot *et al.* (1991) |
| *Lactarius lignyotus* | 100 | $\alpha_4$ | - | 4.0 | | Giollant *et al.* (1993) |
| *Macrophomina phaseolina* | 34 | α | - | 16.4 | N-Acetylneuraminyl N-acetyllactosamine | Bhowal *et al.* (2005) |
| *Peziza sylvestris* | 20 | α | - | - | Arabinose | Wang and Ng (2005) |
| *Pleurotus ostreatus* | 72 | αβ | - | - | | Wang *et al.* (2000) |
| *Pleurocybella porrigens* | 56 | $\alpha_4$ | 5.7 | 2.8 | Asialo-bovine submaxillary mucin | Suzuki *et al.* (2009) |
| *Rhizoctonia solani* | 31 | $\alpha_2$ | >9.0 | 0.0 | | Candy *et al.* (2001), Vranken *et al.* (1987) |
| *Rhizopus stolonifer* | 28 | $\alpha_6$ | -- | -- | | Oda *et al.* (2003) |
| *Xerocomus spadiceus* | 32 | $\alpha_2$ | - | - | | Liu *et al.* (2004) |
| *Schizophyllum commune* | 31.5 | - | - | - | Lactose and N-acetyl-D-galactosamine | Chumkhunthod *et al.* (2006) |
| *Ganoderma lucidum* | 114 | $\alpha_6$ | | 9.3 | Glycoproteins | Thakur *et al.* (2007a, b) |

such as *Phallus impudicus* (Entlicher *et al.*, 1985) and *Lactarius lignyotus* (Sychrova *et al.*, 1985), where subunits are linked together by disulphide linkages. Lectin L1 from *Lentinus edodes* is monomeric having molecular mass 45 kDa (Tsivileva *et al.*, 2008). A lectin, CML from *Cordyceps militaris* is also monomeric with a molecular mass 31 kDa (Jung *et al.*, 2007). The lectins of *Pleurocybella porrigens* (Suzuki *et al.*, 2009) and *Agaricus blazei* (Kawagishi *et al.*, 1988) are homotetrameric, whereas, *Lactarius rufus* lectin (Panchak and Antoniuk, 2007) and *Rhizopus stolonifer* (Oda *et al.*, 2003) are hexameric. The lectin of *Hericium erinaceum* is a heterotetramer with molecular mass of 54 kDa and has two different subunits with molecular mass of 15 and 16 kDa (Kawagishi *et al.*, 1994) and interestingly, a lectin from *Kluyveromyces bulgaricus* forms octamer at high concentration (Al-Mahmood *et al.*, 1991).

**Isoelectric point:** Isoelectric points of majority of fungal lectins are in the range of 5-8 (Table 1). Lectin from *Chlorophyllum molybdites* (Kobayashi *et al.*, 2004) is highly acidic proteins with a pI of 3.75. On the other hand, lectins from *Laccaria amethystea* (Guillot *et al.*, 1983), *Auricularia polytricha* (Yagi and Tadera, 1988) and *Rhizoctonia solani* (Candy *et al.*, 2001) are highly basic proteins with the pI values of 9.5, 10.6 and >9, respectively.

**Carbohydrate content:** The carbohydrate content varies from lectin to lectin and in some cases it could be high as 30% as in *Rigidoporus lignosus* lectin (Guillot and Konska, 1997) while in some cases it is totally absent as in *Laccaria amethystea* (Guillot *et al.*, 1983) and *Laetiporus sulphureus* lectins (Konska *et al.*, 1994) (Table 1).

**Metal ion requirement:** Fungal lectins in general do not require metal ions for their activity. The lectin of *Xerocomus chrysenteron* require $Mn^{2+}$ for its activity (Sychrova *et al.*, 1985). In case of *Xerocomus spadiceus* lectin $Zn^{2+}$ and $Al^{3+}$ stimulated the activity (Liu *et al.*, 2004) while $Fe^{3+}$ stimulated the activity of *Polyporus adusta* lectin (Wang *et al.*, 2003). Contrarily, $Fe^{3+}$, $Al^{3+}$ and $Zn^{2+}$ inhibited activity of *Armillaria luteo-virens* lectin (Feng *et al.*, 2006). Activity of *Pholiota adiposa* lectin is enhanced by $Cu^{2+}$, $Fe^{2+}$ and $Al^{3+}$ (Zhang *et al.*, 2009). The hemagglutinating activity of *Inocybe umbrinella* is inhibited by $Ca^{2+}$, $Mn^{2+}$ and $Mg^{2+}$ but not affected by $Fe^{3+}$, $Zn^{2+}$, $Al^{3+}$ (Zhao *et al.*, 2009). Interestingly, hemagglutinating activity of *Pleurotus citrinopileatus* lectin was inhibited by $HgCl_2$ but enhanced by $AlCl_3$ (Li *et al.*, 2008).

**Stability and denaturation:** Some lectins showed considerable stability such as *Pholiota adiposa* lectin, which is stable upto 50°C and in the low molarity NaOH and HCl solutions (Zhang *et al.*, 2009). Lectin from *Pleurocybella porrigens* is stable below 60°C and pH range 4.5-8.0 (Suzuki *et al.*, 2009), whereas, lectin from ascomycete *Cordyceps militaris* is stable between pH range 2-13 (Wong *et al.*, 2009). The *Agaricus edulis* lectins showed very high thermostability and could withstand high concentration of urea and extreme pH (Eifler and Ziska, 1980). *Ganoderma capense* lectin is stable at 100°C for 60 min (Ngai and Ng, 2004), whereas, *Armillaria luteo-virens* lectin is stable up to 70°C but sensitive to high and low pH (Feng *et al.*, 2006).

*Fusarium solani* lectin was studied for conformation stability at extreme pH, temperature and in the presence urea and guanidine thiocyanate. The lectin showed flexible tertiary structure at low pH but maintain secondary and quaternary structure. In the presence of urea and guanidine thiocyanate, it showed monophasic unfolding curves and its heat capacity remained constant during thermal denaturation (Khan *et al.*, 2007a).

**Fluorometric property:** In *Agrocybe cylindracea* lectin fluorescence quenching and modification of tryptophan residues indicated that there were about two tryptophan residues in the protein and one of them might be located on the surface, while the other was buried in the hydrophobic shallow groove near the surface (Liu *et al.*, 2008). In case of *Fusarium solani* lectin fluorescence quenching revealed that the single tryptophan in the subunit is 100% accessible to acrylamide but only 50% to succinimide and effect of pH on iodide and cesium induced quenching indicated that the tryptophan residue might be present in vicinity of positively charged amino acids (Khan *et al.*, 2010).

**Chemical modification:** Chemical modification studies of *Ischnoderma resinosum* lectin showed involvement of lysine, carboxylate, arginine, tryptophan, histidine, cysteine and tyrosine in the binding activity of the lectin. Inhibitory sugar of the lectin viz. lactulose could not protect inactivation against NBS mediated modification, whereas, it protected inactivation induced by glycine ethyl ester, cyclohexane-1,2-dione, ethoxyformic anhydride and N-acetylimidazole (NAI) (Kawagishi and Mori, 1991). Tryptophan, carboxylate and tyrosine have been implicated in the binding activity of the lectin form *Hericium erinaceum* (Gong *et al.*, 2004).

Chemical modification of serine/threonine and histidine showed the partial necessity of these residues for the hemagglutinating activity of *Agrocybe cylindracea* lectin. However, modifications of arginine, tyrosine and cysteine residues had no effect on its hemagglutinating activity (Liu *et al.*, 2008). In case of *Fusarium solani* lectin only tyrosine residues were found to involve in hemagglutinating activity of the lectin and the inactivation caused by modification of tyrosine by N-acetylimidazole (NAI) was reversed by hydroxylamine (Khan *et al.*, 2010). Tryptophan, lysine and histidine have been implicated in the hemagglutinating activity of *Ganoderma lucidum* lectin (Thakur *et al.*, 2007b).

**Agglutination:** Lectins are recognized by their important property to agglutinate various types of cells such as erythrocytes. Some of the fungal lectins showed discrimination between erythrocytes of different blood groups. Treating erythrocytes with proteolytic enzymes can enhance their activity or modify specificity (Guillot and Konska, 1997). In some cases higher specific activity was observed with trypsinized (Konska, 1988) or pronase treated erythrocytes (Khan *et al.*, 2007c). Some lectin showed distinction among human blood group types, e.g., *Marasmius oreades* lectin specifically agglutinates blood group B erythrocytes (Grahn *et al.*, 2007).

In some cases only animal erythrocytes were agglutinated and some lectins can also discriminate among different animal erythrocytes. Lectins from few *Aspergillus* species were found to agglutinate human and pig erythrocytes but not sheep or goat erythrocytes (Singh *et al.*, 2008). A lectin from *Cordyceps militaris* can agglutinate mouse and rat erythrocytes but not human ABO erythrocytes (Jung *et al.*, 2007). *Pleurocybella porrigens* lectin showed good activity with human ABO pronase and neuraminidase treated erythrocytes, but no activity with untreated erythrocytes, it could also distinguish between mouse and rat erythrocytes (Suzuki *et al.*, 2009). Several other erythrocytes from mammals, birds, reptiles and amphibians have also been used for hemagglutination (Kawagishi *et al.*, 1994; Panchak and Antoniuk, 2007; Stepanova *et al.*, 2007).

**Carbohydrate specificity:** Fungal lectins exhibit broad carbohydrate specificity, varying from simple sugars to glycoproteins. *Peziza sylvestris* (Wang and Ng, 2005) lectin is specific for arabinose while *Hericium erinaceus* lectin (Kawagishi *et al.*, 1994) is specific for sialic acid (Table 1). Several

techniques are used to determine carbohydrate specificity such as simple and conventional hemagglutination inhibition (Khan *et al.*, 2007c) to more advanced glycan microarray (Pohleven *et al.*, 2009), enzyme linked lectinsorbent assay (Wu *et al.*, 2001) and frontal affinity chromatography (Van Damme *et al.*, 2007). The hemagglutinating activity of *Grifola frondosa* lectin was inhibited only by the homogeneous preparation of a polysaccharide, linear D-rhamnan (Stepanova *et al.*, 2007). The hemagglutinating activity of *Pleurotus citrinopileatus* lectin was inhibited by maltose, O-nitrophenyl-β-D-galactopyranoside, O/P-nitrophenyl-β-D-glucuronide and insulin (Li *et al.*, 2008). Glycan microarray analysis revealed that the *Clitocybe nebularis* lectin recognizes human blood group A determinant GalNAcα1-3(Fucα1-2)Galβ-containing carbohydrates and GalNAcβ1-4GlcNAc (N,N'-diacetyllactosediamine) (Pohleven *et al.*, 2009). Frontal affinity chromatography revealed that the binding site of *Sclerotinia sclerotiorum* agglutinin primarily accommodates a non-reducing terminal GalNAc (Van Damme *et al.*, 2007). Among glycoproteins tested for binding, *Sclerotium rolfsii* lectin reacted strongly with GalNAcα1→Ser/Thr (Tn) and/or Galβ1→3GalNacα1→($T_\alpha$) containing glycoproteins such as human $T_\alpha$ and Tn glycophorin, asialo-BSM, asialo-PSM and asialofetuin, but its reactivity towards sialated glycoprotein was reduced significantly (Wu *et al.*, 2001).

Some other lectins showed specificity for unusual carbohydrates, e.g. mushroom lectin *Xylaria hypoxylon* for inulin and xylose (Liu *et al.*, 2006), *Agrocybe Cylindracea* lectin for sialic acid (Wang *et al.*, 2002; Yagi *et al.*, 1997), *Polyporus adusta* lectin for turanose (Wang *et al.*, 2003), *Peziza sylvestris* lectin for arabinose (Wang and Ng, 2005), whereas hemagglutinating activity of *Lyophyllum shimeiji* lectin could not be inhibited by simple sugars and glycoproteins (Ng and Lam, 2002).

Interestingly, the lectin *Pleurotus ostreatus* was also found to have α-galactosidase activity, the enzyme activity and carbohydrate binding property was not due to same site since the lectin accepts both α- and β-glycosides, whereas the enzyme activity was restricted to the α-anomer only. Moreover, the α-galactosidase activity was inhibited by α-galactose but not by β-galactose (Brechtel *et al.*, 2001).

**Affinity constants ($K_a$) and thermodynamics of interactions with carbohydrates:** The kinetic data for binding of lectins to carbohydrate ligands are available for few fungal lectins. Several modern techniques such as surface plasmon resonance (SPR) have been used, which involves immobilization of either lectin (Khan *et al.*, 2007c) or ligand (Suzuki *et al.*, 2009). Affinity constants have been determined for the *Fusarium solani* lectin using spectrofluorometry (Khan *et al.*, 2007b) and surface plasmon resonance (SPR) (Khan *et al.*, 2007c), the lectin showed very low affinity constants for mono- and oligosaccharides but showed very high affinity constants for glycoproteins such as asialo-mucin ($K_a$ = 1.61 e10 $M^{-1}$). The binding was exothermic and enthalpically driven. The association rate constants were several orders magnitude slower than diffusion controlled reactions (Khan *et al.*, 2007c). Affinity of *Ganoderma lucidum* lectin for glycoproteins was also explored using SPR, it was observed that the affinity for N-glycans was two order higher than O-glycans (Thakur *et al.*, 2007a).

In SPR studies, the dimeric *Aleuria aurantia* lectin (AAL) found to have 5 binding sites per subunit and one binding site in recombinant AAL had unusually high affinities towards fucose and fucose-containing oligosaccharides with $K_D$ values in the nanomolar range (Olausson *et al.*, 2008). Comparative binding study of *Aleuria aurantia* lectin (AAL) and *Aspergillus oryzae* lectin (AOL) employing frontal affinity chromatography revealed that AOL showed 2.9-6.2 times higher affinity

constants ($K_a$) for α-1,6-fucosylated oligosaccharides than AAL and only AAL, additionally recognized oligosaccharides which were α-1,3-fucosylated at the reducing terminal GlcNAc (Matsumura *et al*., 2009). Isothermal titration calorimetry (ITC) measurements carried out for CGL3, lectin from *Coprinopsis cinerea,* indicated strongly enthalpically driven binding for chitotriose (Walti *et al*., 2008).

**Amino acid composition:** *Pleurocybella porrigens* lectin showed high amounts of ASX (12.4%), Thr (11.2%), Leu (8.8%) but complete absence of Cys, Met and Lys (Suzuki *et al*., 2009). Similarly, the amino acid analysis of the *Grifola frondosa* lectin showed a greater percentage of amino acids with positively charged R groups, arginine, lysine and histidine, but complete absence of sulfur-containing amino acids, cysteine and methionine (Stepanova *et al*., 2007). Lectin L2 isolated from *Lentinus edodes* contains high amount of Asn, i.e., 42% (w/v) (Tsivileva *et al*., 2008). The lectin from *Ischnoderma resinosum* contained substantial amounts of acidic and hydroxy amino acids, glycine, valine and leucine, but minute quantities of methionine, histidine and arginine (Kawagishi *et al*., 1988). The *Fusarium solani* lectin showed high amount of Gly and Lys, but very low amount of Trp and Cys (Khan *et al*., 2007c).

**Amino acid sequence homology:** The amino acid sequence of *Xerocomus chrysenteron* lectin showed 69 and 64% homology with *Agaricus bisporus* and *Arthrobotrys oligospora* (Birck *et al*., 2004). The N-terminal sequence of *Pholiota adiposa* lectin showed little similarity to sequence of Agaricales lectins (Zhang *et al*., 2009). The amino acid sequence of *Pleurocybella porrigens* lectin showed similarity with ricin-B-chain (33%), lectin from *Polyporus squamosus* (36%) and hemagglutinin from *Clostridium botulinum,* HA-1 (40%) (Suzuki *et al*., 2009). The sequence homology and structure prediction revealed that *Clitocybe nebularis* lectin belongs to ricin B-like superfamily (Pohleven *et al*., 2009). The N-terminal sequence of *Inocybe umbrinella* lectin (Zhao *et al*., 2009), *Fusarium solani* lectin (Khan *et al*., 2007c) and *Pleurotus citrinopileatus* lectin (Li *et al*., 2008) did not show similarity to any know lectin or hemagglutinin, whereas N-terminal sequence of *Pleurotus tuber-regium* lectin showed some similarity to that of *Agaricus bisporus* lectin (Wang and Ng, 2003). The deduced amino acid sequence of *Grifola frondosa* lectin showed 26.1 and 22.8% homology with jacalin related plant lectins from *Helianthus tuberosus* and *Parkia platycephala* (Nagata *et al*., 2005). On the other hand, *Sclerotinia sclerotiorum* lectin showed significant similarity only to the lectin from the fungus *Ciborinia camelliae* but not with any other lectins (Candy *et al*., 2003) (Fig. 1A, B).

**Structure:** *Aleuria aurantia* was the first fungal lectin to solve the crystal structure. The crystal structure of the lectin complexed with fucose revealed that each monomer consists of a six-bladed β-propeller fold and a small antiparallel two-stranded β-sheet that plays a role in dimerization (Wimmerova *et al*., 2003). The six-bladed β-propeller structure was also found to have three bound fucose residues (Fujihashi *et al*., 2003), suggesting that the binding sites, although all very similar in geometry, do not have the same affinity for ligands. *Flammulina velutipes* lectin showed unique folds never before observed in lectins (Paaventhan *et al*., 2003) and showed structural similarity to human fibronectin and lectins from *Xerocomus chrysenteron* (Birck *et al*., 2004) and *Agaricus bisporus* (Carrizo *et al*., 2005), resembling actinoporins, a family of pore-forming toxins from sea anemones. CGL2 from *Coprinus cinerea* showed fold similar to galectins (Vasta *et al*., 2004), a large family of lectins from all classes of vertebrates (Walser *et al*., 2004). The lectin from *Laetiporus*

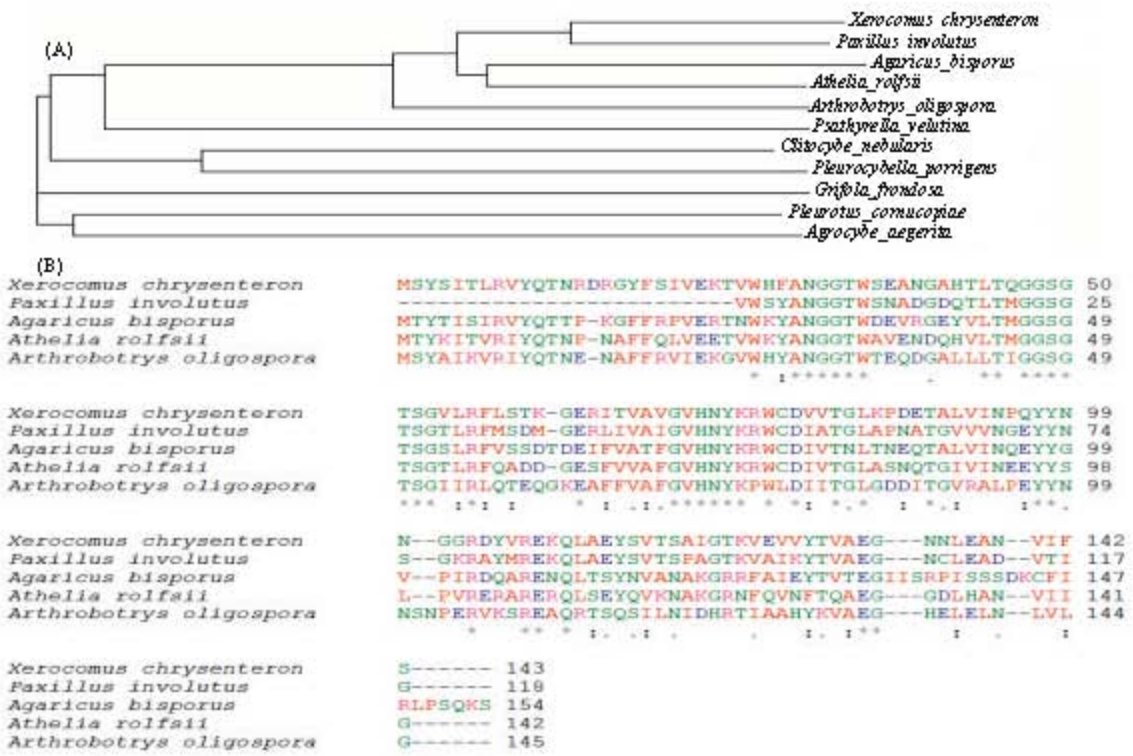


Fig. 1: (A) Phylogenetic tree (B) and sequence alignment of some related fungal lectins. Conserved residues have been marked by stars at bottom. Amino acid sequences of the lectins were obtained from NCBI (http://www.ncbi. nlm.nih.gov/protein) and aligned by ClustalW2 (http://www.ebi.ac.uk/Tools/clustalw2/index.html)

*sulphureus* (Mancheno *et al*., 2005) showed resemblance with the ricin-B domain, a trefoil-based fold observed in many lectins and carbohydrate-binding domains and referred to as the (QxW)3 domain (Hazes, 1996). This lectin assembles as a trimer, each monomer consisting of a ricin-B domain and an elongated domain with structural similarity to aerolysin, a bacterial β-pore-forming toxin. This domain could be directly involved in pore formation because the lectin displays hemolytic activity (Tateno and Goldstein, 2003). The ricin-like domain displayed structural similarity to similar domains from plant toxins (ricin, abrin and mistletoe lectin), but was even more similar to the hemagglutinin component of bacterium *Clostridium botulinum* (Inoue *et al*., 2003). Structural comparison of the (QxW)3 domains from mushroom toxin, clostridial hemagglutinin and ricin illustrated their high similarity. During evolution, this domain has been conserved and often duplicated and/or combined with other domains. It has been identified in bacteria, fungi and plants and also in sponge, insects and mammals, generally conserving its role of targeting a sugar-coated substrate (Hazes, 1996).

*Agrocybe aegerita* lectin showed structural similarity with galectins, the carbohydrate recognition domain (CRD) of which contains consensus sequence motif, which consists of His-44, Arg-48, Val-59, Asn-61, Trp-68, Glu-71 and Arg-73 (Yang *et al*., 2005b), later it was found that in dimeric *Agrocybe aegerita* lectin each protomer adopts a prototype galectin fold (Yang *et al*., 2009).

Structure of *Marasmius oreades* agglutinin (MOA), was solved in complex with blood group B trisaccharide at 1.8 resolution. It was found that the carbohydrate ligand binds to all three binding sites of N-terminal β-trefoil domain. The structure was solved in the presence of $Ca^{2+}$ which binds to MOA dimer and alters the conformation of the C-terminal domain by opening up the cleft containing a putative catalytic site (Grahn *et al*., 2007, 2009).

*Sclerotium rolfsii* lectin (SRL) crystals were grown by the hanging-drop vapor diffusion method, which belongs to the tetragonal space group $P4_22_12$ group (Leonidas *et al*., 2003). The crystal structure the lectin in its free form and in complex with N-acetyl-D-galactosamine (GalNAc) and N-acetyl-D-glucosamine (GlcNAc) has been determined at 1.1 A, 2.0 A and 1.7 A resolution, respectively. The protein structure is composed of two beta-sheets, which consist of four and six beta-strands, connected by two alpha-helices. Sequence and structural comparisons revealed that SRL is the third member of a newly identified family of fungal lectins, which includes lectins from *Agaricus bisporus* and *Xerocomus chrysenteron* that share a high degree of structural similarity and carbohydrate specificity (Leonidas *et al*., 2007). Ambiguity in X-ray structure regarding Glx and Asx was solved by mass spectrometry in *Sclerotium rolfsii* lectin (Sathisha *et al*., 2008).

Crystal structure of the lectin from the mushroom *Psathyrella velutina* showed that it adopts a very regular seven-bladed beta-propeller fold with the N-terminal region tucked into the central cavity around the pseudo 7-fold axis (Cioci *et al*., 2006). *Sclerotinia sclerotiorum* agglutinin, based on molecular modeling, is expected to constitute a novel lectin family (Van Damme *et al*., 2007).

**Cloning and site directed mutagenesis:** The cDNA for *Agrocybe aegerita* lectin was prepared from total RNA using RT-PCR, cloned and expressed in BL-21 (DE3) strain of *Escherichia coli* (Yang *et al*., 2005a). The cDNA of the *Pleurocybella porrigens* lectin was cloned and sequenced (Suzuki *et al*., 2009).

Site-directed mutagenesis carried out in *Aleuria aurantia* lectin showed that in β-2 mutant, out of five binding sites, substitution of $Tyr^{26}$ (Site 1), $Tyr^{79}$ (Site 2) and $Tyr^{181}$ (Site 4) with Val resulted in loss of hemagglutinating activity, whereas mutation at $Tyr^{133}$ (Site 3) and $Tyr^{228}$ (Site 5) did not cause any loss of activity (Amano *et al*., 2004). In the case of AAL (*Agrocybe aegerita* lectin) 11 mutants were prepared, which concluded that dimerization of the lectin is essential for its tumor cell apoptosis-inducing activity. A hydrophobic pocket consisting $Leu^{33}$, $Leu^{35}$, $Phe^{93}$ and $Ile^{44}$ was found to be involved in conferring the tumor cell apoptosis-in ducing activity. Single mutant such as Phe93Gly or Ile114Gly didn't disrupt carbohydrate binding and homodimerization capabilities, but abolished the bioactivity of the lectin (Yang *et al*., 2009). *Coprinopsis cinerea* lectin, CGL3, showed homology with galectins with all but one conserved residues: Arg and mutation of this residue to Trp (R81W) changed its specificity from chitooligosaccharides to lactose (Walti *et al*., 2008).

**Biological role:** Lectins, due to their ability to recognize different structures, constitute an important element of biological system. Their physiological role is related with the identification of glycosylated structures at the level of cells, tissues and the whole organisms. Some of their biological roles have documented earlier, such as participate in the formation of primordia, creation of mycelium structures to facilitate, penetration of parasitic fungi into the host organism as well as mycorrhization, introducing morphological changes in host and in dormancy (Guillot and Konska, 1997; Konska, 2006).

**Growth and morphogenesis:** A lectin may be involved in ensuring cohesion between hyphae during the development of the basidiome as seen in *Pleurotus cornucopiae* (Kaneko *et al*., 1993). Paracoccin is an N-acetyl-glucosamine-binding lectin from *Paracoccidioides brasiliensis*, Immunoelectron microscopy with mouse anti-paracoccin IgG localized the antigen to the cell wall of *P. brasiliensis* yeast forms. Paracoccin interacted with chitin and colocalized with beta-1,4-homopolymer of GlcNAc to the budding sites of *P. brasiliensis* yeast cell. When the yeast cells were cultivated in the presence of anti-paracoccin antibodies, a significant reduction of both colony forming units and individual yeast cells as well as morphological alterations such as smaller colonies were observed. It was concluded that binding of specific antibodies to paracoccin may disrupt the paracoccin/chitin interactions, resulting in the inhibition of *P. brasiliensis growth* (Ganiko *et al*., 2007). *Lactarius deterrimus* lectin was produced by cultured mycelia and could be localized by immuno-fluorescence in the cell wall. Receptors for the lectin were localized on the root hairs of axenically grown spruce seedlings. This inferred a role of the fungal lectin in recognition and specificity during the early stages of mycorrhiza formation (Giollant *et al*., 1993). Activity of *Lentinus edodes* intracellular lectins varied at various developmental stages of the fungus, the specific activity increased in brown mycelium film stage exceeded the corresponding value for nonpigmented mycelium (Vetchinkina *et al*., 2008).

The role of CGL1 and CGL2, lectins from *Coprinopsis cinerea*, in tissue development was studied by Walser *et al*. (2004, 2005). The developmentally regulated ligands for galectins were co-localized with the galectin expression, in the veil surrounding the developing primordium and the outer cells of the young stipe. In addition, galectin ligands were observed in the hymenium. The subcellular localization of the galectin ligands suggested these to be present in the cellular compartments distinct from galectin transport. The sensitivity of *in situ* interactions with exogenous galectins towards detergents and organic solvents inferred that these ligands were lipid-borne. Accordingly, lipid fractions from primordia were shown to contain galectin-binding compounds. Based on these observations it was hypothesized that β-galactoside-containing lipids (basidiolipids) found in mushrooms are the physiological ligands for the galectins in *C. cinerea* (Walser *et al*., 2005).

It was speculated that the *Aspergillus fumigatus* lectin may contribute to the attachment of conidia to the extracellular matrix components through the recognition of the numerous terminal sialic acid residues of their carbohydrate chains (Tronchin *et al*., 2002).

**Involved in pathogenesis:** Paracoccin, a GlcNAc-binding lectin with a molecular mass 160 kDa, purified from human pathogen *Paracoccidioides brasiliensis*, bind to laminin and induced TNF-alpha production by macrophages (Coltri *et al*., 2006).

**Molecular recognition:** Presence of lectins, with strict specificities, in fungal cells of ectomycorrhizal symbiosis, suggests that lectins might be involved in recognition between the tree and its symbiont (Giollant *et al*., 1993).

Some of the molecules present in the soil can combine with fungal lectins and block their specific binding sites and in the rhizosphere, *e.g.* certain phenolic acids that can modify carbohydrate receptors on the roots of the host trees, will prevent recognition and consequently mycorrhization (Guillot *et al*., 1994).

TBF-1, the main soluble protein in the *Tuber borchii* fruiting body that is able selectively to bind the exopolysaccharides produced by ascoma-associated *Rhizobium* sp. was found to a phase-specific lectin, involved in molecular recognition (Cerigini *et al*., 2008).

**Self defense against predator:** Feeding of a mushroom galectin, *Coprinopsis cinerea* CGL2, to the namatode *Caenorhabditis elegans* inhibited development and reproduction and ultimately resulted in killing of the host. The lack of toxicity of a carbohydrate-binding defective CGL2 variant and the resistance of a *C. elegans* mutant defective in GDP-fucose biosynthesis suggested that CGL2-mediated nematotoxicity depends on the interaction between the galectin and a fucose-containing glycoconjugate. These results indicated a possible role of fungal galectins in defense of fungi against predators by binding to the specific glycoconjugates of the hosts (Butschi *et al*., 2010).

**Applications:** Ability of lectins to interact with simple, aminated, acetylated, sialated and complex carbohydrates has been exploited for typing blood cells, carrier for chemotherapeutic agents, mitogens, fractionation of animal cells, or for studying cellular surfaces. They have been used for the isolation and purification of the serum glycoconjugates, identification and differentiation of various microorganisms and in cell sorting. They have also been successfully utilized as epidemiologic as well as taxonomic markers of specific microorganism (Guillot and Konska, 1997; Slifkin and Doyle, 1990).

**As biomarker:** Fungal lectin have been used to study glycoconjugates, involved in the cellular interactions during the uro-genital morphogenesis in bird embryos, to understand the mechanisms responsible for the migration of germ cells. In birds, the primordial germ cells (PGCs), localized at the primitive line stage in the Swift crescent, subsequently migrate *via* the bloodstream towards future genital ridges. There are many arguments in favor of involvement of membrane glycoproteins in the mechanisms of recognition between PGCs and tissues during the migration. FITC-labeled lectins and NC-1/HNK-1 mono-clonal antibodies used in indirect fluorescence reactions bind to PGCs and afford ready visualization. The lectin of *Laetiporus sulphureus,* which recognizes N-acetyllactosamine residues is one of the most specific to this cell type (Didier *et al*., 1984, 1990; Fargeix *et al*., 1980).

Surface plasmon binding studies carried for *Aspergillus oryzae* lectin towards 1-fucose containing chains, indicated that it has strongest preference for the alpha1,6-fucosylated chain among alpha1,2-, alpha1,3-, alpha1,4- and alpha1,6-fucosylated pyridylaminated (PA)-sugar chains. Moreover positive staining of *Aspergillus oryzae* lectin, but not *Aleuria aurantia* lectin, was completely abolished in the cultured embryo fibroblast (MEF) cells obtained from alpha1,6-fucosyltransferase (Fut8) knock-out mice, as assessed by cytological staining, suggested that *Aspergillus oryzae* lectin is more suitable for detecting core fucose than *Aleuria aurantia* lectin or *Lens culimaris* agglutinin-A (Matsumura *et al*., 2007).

**In cancer research:** Clitocybe nebularis lectin elicited antiproliferative effect on human leukemic T cells (Pohleven *et al*., 2009). The AAL (*Agrocybe aegerita* lectin) possesses a potent tumor-suppressing function against several human tumor cell lines, including HeLa, SW480, SGC-7901, MGC80-3, BGC-823 and HL60, as well as the mouse sarcoma cell line S-180. It can also inhibit the viability of S-180 tumor cell *in vivo*. It also displayed apoptosis-inducing activities for cancer cells, indicating that the lectin exerts its antitumor abilities stemming from apoptosis-inducing activities (Zhao *et al*., 2003). The lectin was further found to translocate in the nucleus and induce cell apoptosis. Among the several mutants, dimer interface mutant I25G, carbohydrate recognition

domain (CRD) mutant R63H and loop region mutant L33A could not enter the nucleus and lost the ability to induce apoptosis (Liang *et al*., 2009). *Boletus satanas* lectin inhibited DNA and protein synthesis in Maidn Darby canine kidney cells with an $IC_{50}$ of 0.62 and 0.14 μM, respectively and the inhibitory effects could be reversed by addition of the galactose (Kretz *et al*., 1991).

The *Pleurotus citrinopileatus* lectin exerted potent antitumor activity in mice bearing sarcoma 180 and caused approximately 80% inhibition of tumor growth when administered intraperitonealy at 5 mg $kg^{-1}$ daily for 20 days. It also elicited a mitogenic response from murine splenocytes *in vitro* with the maximal response at a lectin concentration of 2 μM (Li *et al*., 2008). Similarly, lectin of *Pleurotus ostreatus* also exerted potent antitumor activity in mice, bearing sarcoma S-180 and hepatoma H-22 cells. Survival in these mice was prolonged and body weight increase reduced after lectin treatment (Wang *et al*., 2000). There are several lectins which show antiproliferative activities towards several cells such as *Pholiota adiposa* lectin (Zhang *et al*., 2009), *Inocybe umbrinella* lectin (Zhao *et al*., 2009), *Schizophyllum commune* lectin (Han *et al*., 2005), *Tricholoma mongolicum* lectin (Wang *et al*., 1995) and *Xerocomus spadiceus* lectin (Liu *et al*., 2004).

The *Volvariella volvacea* lectin also demonstrated immunomodulatory activity as a potent stimulatory activity towards the murine splenic lymphocytes. It was also found to markedly enhance the transcriptional expression of interleukin-2 and interferon-gamma by reverse transcriptase-polymerase chain reaction. As revealed by its N-terminal amino acid sequence, it was distinct from other immunomodulatory proteins previously reported (Hsu *et al*., 1997) and VAG (Lin and Chou, 1984) from the same fungus.

**In AIDS research:** Some fungal lectins were also tested for their potential inhibitory effect against HIV. The fungal lectins from *Pleurotus citrinopileatus* inhibited HIV-1 reverse transcriptase with an $IC_{50}$ of 0.93 μM (Li *et al*., 2008).

**As bio-insecticide:** In some cases fungal lectins were found to exhibit insecticidal activity, which renders their use as bio-insecticide. *Myzus persicae* a polyphagous aphid, showed no significant differences of mortality when fed with the XCL (*Xerocomus chrysenteron* lectin) associated with Glucose and Mannose or fed on XCL diet only. At the opposite, the mortality rates related to artificial diet supplemented with Galactose or GalNAc and XCL were significantly reduced. There was then a significant mortality difference between *M. persicae* fed on an artificial diet incorporated specific carbohydrate binding Lectin with those fed with lectin only, it concluded that XCL can show potential insecticidal activity in the absence of inhibitory sugars (Jaber *et al*., 2006, 2007, 2008).

## CONCLUSIONS

The fungal lectins, reported so far, still constitute a minority among carbohydrate interacting proteins and hemagglutinins. In the light of diverse information obtained about their functions and biological roles, it is difficult to say whether they are present ubiquitously among fungi, or restricted to only some selected members among 1.5 million fungal species. Availability of more sequence information of the fungal lectin and fungal genomes, in the future will be able to make more assumptions about their origin and evolution.

On the other side, fungal lectins have also been seen as promising candidates for targeted drug delivery; however, such a use requires engineered lectin molecules with precisely defined specificity. That can be only be achieved by clubbing information for all the carbohydrate binding proteins.

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